IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Kemmerer, Elizabeth
	)	
ASHKENAZI, et al.	)	Art Unit: 1646
	)	
Application Serial No. 09/904,766	)	Confirmation No: 4054
	)	
Filed: July 12, 2001	)	Attorney's Docket No. 39780-1618 P2C33
	)	
For: **PRO269 POLYPEPTIDES**	)	**Customer No.** 77845

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES APPELLANTS' REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On November 1, 2006, the Examiner made a Final rejection to pending Claims 44-46 and 49-52. A Notice of Appeal was filed on May 1, 2007, and an Appellants' Appeal Brief was filed August 29, 2007.

An Examiner's Answer was mailed on January 9, 2008. The following constitutes Appellants' Reply Brief in response to the Examiner's Answer and is timely filed since March 9, 2008 was a Sunday. This Reply Brief is accompanied by a Request for Oral Hearing.

ARGUMENTS

I. *Claim Rejections Under 35 U.S.C. §101 and §112, First Paragraph*

Concerning the rejection of Claims 44-46 and 49-52 under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible asserted utility or a well established utility, in her Answer, the Examiner cites the following arguments:

(1) The instant rejections are primarily based on whether or not genomic DNA levels (as measured by the gene amplification assay) correlate with either mRNA levels or polypeptide levels. The Examiner says that the Polakis I and II Declarations filed under 37 CFR 1.132 filed on 03 November 2004 and 30 March 2006 respectively, are limited to an issue that is no longer relevant (i.e.: mRNA levels are most likely predictive of polypeptide levels) in the instant case. In addition, the Examiner asserts that the fact pattern in the Board Decision (Appeal No. 2006-1469), where the microarray assay was the issue, differs significantly from the instant gene amplification case. The Examiner says that there were several critical pieces of evidence supporting the Appellant's position in the microarray cases; for example, multiple declarations, including high probative declarations containing further data. The Examiner alleges that she does not find such preponderance of evidence in support of the position that increased genomic DNA levels correlate with increased polypeptide levels (page 11 of the Examiner's answer).

(2) The Examiner did not find the Goddard declaration persuasive and says that "it is off-point" since the claims are directed to PRO269 polypeptides, not PRO269 genes (Examiner's Answer, page 12). The Examiner adds that the Goddard Declaration speaks to the utility and enablement of genes, not of the encoded polypeptides in cancerous tissues (page 15 through page 16). The Examiner addresses the pooled blood controls used in the gene amplification assay and asserts that the controls were not matched, non-tumor lung samples, but rather pooled DNA samples from blood of healthy subjects. The Examiner insists that the art (allegedly, Pennica *et al.*, Konopka *et al.*) used matched tissue samples (page 15 of Examiner's Answer).

(3) The Examiner alleges that the Ashkenazi declaration actually supports the Examiner's position (page 11, last two lines of the Examiner's answer) in that it provides further evidence that gene amplification does not correlate with increased mRNA/polypeptide levels (page 16 of the Examiner's answer).

(4) Of the over 100 supportive references submitted by the Appellants during prosecution, the Examiner insists that none of these references address the issue of whether or not gene amplification correlates with increased mRNA/polypeptide levels (page 16 of Examiner's Answer). Regarding the supportive references Orntoft *et al.*, Hyman *et al.* and Pollack *et al.*, made of record by the Appellants, and which clearly address gene amplification, the Examiner considers them flawed. The reasons cited were: Orntoft *et al.* only compared levels of about 40 well-resolved an focused on abundant proteins; Hyman *et al.* found 44% of highly amplified genes showed overexpression at the mRNA level, and 10.5% of highly overexpressed genes were amplified and even at this level of high amplification and high overexpression, the two did not correlate; Pollack *et al.* is also limited to highly amplified genes and used a different method to evaluate their results (pages 12-13 of Examiner's Answer).

Moreover, the Examiner asserts that references such as Sen, Godbout *et al.*, Bea *et al.* and Li *et al.* constitute strong opposing evidence for the claimed polypeptides having utility and enablement, based on the presumption that the claimed polypeptides are also overexpressed following gene amplification (page 15 of the Examiner's Answer). Referring to Sen, the Examiner alleges that, in general, non-cancerous epithelial tissues are frequently aneuploid, and thus an increase in genomic DNA is not diagnostic of cancer. The Examiner also quotes Godbout as stating: "*It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to a cell...*" and thereby inquires whether Appellant can show evidence for PRO269 providing a selective growth advantage to a cell (page 17 of Examiner's Answer). The Examiner also asserts that PRO269 is not a putative oncogene and that the function of the encoded polypeptide is not known (page 18 of Examiner's Answer).

(5) Based on the Pennica *et al.* and Konopka *et al.* references, the Examiner asserts that these references constitute evidence that it cannot be assumed that amplified genomic DNA results in overexpressed gene product (Examiner's answer, pages 16-17 onwards).

Appellants strongly disagree with each of the Examiner's arguments on a number for grounds. The Examiner's arguments will be addressed in the order they are listed above.

Reply to the Examiner's arguments

(1) and (2) The Goddard Declaration was presented to show what ΔCt values were considered significant in the TaqMan™ assay. The ΔCt values for the DNA that encodes for PRO269 showed **2-3.5 fold amplification in 8 primary lung tumors and tumor cell lines**, which would be considered significant according to the Goddard Declaration. While this declaration addresses DNA values, it has been presented in this polypeptide case in conjunction with several other supportive references like Orntoft et al., Hyman et al., Pollack et al., Bea et al., Godbout et al., etc. As explained previously, Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* were presented to show that in general, gene amplification increases mRNA expression. In addition, Appellants presented two Polakis Declarations (Polakis I and II) to show that, in general, mRNA levels correlate well with protein levels, and the Examiner seems to agree with this point especially in view of the recent Board Decision (Decision on Appeal No. 2006-1469) addressing microarray cases. Presentation of the Goddard Declaration is indeed relevant in this polypeptide case, because it forms a critical piece of evidence in this case. When placed together with the entire evidence presented for PRO269, one would logically come to the conclusion that, it is more likely than not, that increased DNA levels generally correlate well with increased mRNA levels (based on, for example, the teachings of supportive references like Orntoft et al., Hyman et al., Pollack et al., Bea et al., Godbout et al., etc.), and further, increased mRNA levels generally correlate well with increased protein levels (the two Polakis Declarations and the recent Board decision). In summary, just as in the microarray cases, Appellants have presented multiple pieces of evidence, such as the Goddard Declaration, the Ashkenazi Declaration, two Polakis Declarations, several references addressing the relationship between DNA and mRNA/ protein levels, etc., each of which is critical evidence that supports their position that PRO269 polypeptides have utility based on the gene amplification results. Therefore, Appellants believe that a sound case has been presented for utility of PRO269 as a diagnostic marker, based on the gene amplification data of its corresponding gene in the specification.

Regarding the rejection of pooled controls (addressed in the Goddard Declaration), Appellants respectfully submit that the Pennica *et al.* and Konopka references do not teach matched controls as the Examiner contends. In fact, Pennica *et al.* teaches the exact same "pooled normal blood controls" as that used in the instant gene amplification assay (for instance,

see page 14718, column 1 and Figure 5 of Pennica *et al.*). Further, the references Bieche *et al.* and Pitti *et al.*, submitted as Exhibits F and G with the Goddard Declaration, also used "pooled normal blood controls" as control. For instance, in Pitti *et al.* the authors used the same quantitative TaqMan PCR assay and pooled normal blood controls described in the instant specification, to study gene amplification in lung and colon cancer of DcR3, a decoy receptor for Fas ligand. Pitti *et al.* analyzed DNA copy number "in genomic DNA from 35 primary lung and colon tumors, relative to pooled genomic DNA from peripheral blood leukocytes (PBL) of 10 healthy donors." (Page 701, col. 1). The authors also analyzed mRNA expression of DcR3 in primary tumor tissue sections and found tumor-specific expression, confirming the finding of frequent amplification in tumors, and confirming that the pooled blood sample was a valid negative control for the gene amplification experiments. In Bieche *et al.*, the authors used the quantitative TaqMan PCR assay to study gene amplification of myc, ccnd1 and erbB2 in breast tumors. As their negative control, Bieche *et al.* used normal leukocyte DNA derived from a small subset of the breast cancer patients (page 663). The authors note that "[t]he results of this study are consistent with those reported in the literature" (page 664, col. 2).

Thus, contrary to the Examiner's allegations, Pennica *et al,* Pitti *et al.* and Bieche *et al.* in fact, confirm the validity of use of the "pooled blood control" as a negative controls, and indicate that this control was widely utilized in the art at the time of filing of the instant application.

(3) The Examiner alleges that the Ashkenazi Declaration actually supports the Examiner's position in that it provides further evidence that gene amplification does not correlate with increased mRNA/polypeptide levels. This position of the Examiner is based on a complete misinterpretation of the Ashkenazi Declaration, its teachings and the arguments presented by the Appellants regarding this Declaration. Appellants fail to see how the Ashkenazi Declaration could support the Examiner's arguments when Appellants clearly stated that, even if there were no correlation between gene amplification and increased mRNA/protein expression, (**which Appellants expressly do <u>not</u> concede to**), a polypeptide encoded by a gene that is amplified in cancer would <u>still</u> have a specific, substantial, and credible utility. Appellants submit that, based on the teachings of the Ashkenazi Declaration and the Hanna and Mornin reference (both previously made of record), one of skill in the art would have known that simultaneous testing of

gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, were not to be over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu. Again, the presentation of this explanation in support of utility is not to be interpreted as a submission of a lack of correlation between DNA and/or mRNA/ protein levels.

(4) The Examiner insists that none of the over 100 supportive references submitted by the Appellants during prosecution address the issue of whether or not gene amplification correlates with increased mRNA/polypeptide levels. Appellants respectfully disagree. At least references Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, Bea *et al.*, Godbout *et al.* were presented during prosecution to show that, in general, gene amplification increases mRNA expression. Besides, as acknowledged throughout prosecution that, in certain references, DNA/ mRNA and protein levels did not correlate, and in fact, Appellants included several such references directed towards a single gene or genes that lack a correlation. This included references that studied single genes or gene families, multiple or large families of genes, and included studies that a wide variety of techniques, including gene amplification and microarray. Regardless of the techniques employed, **by and large**, increased gene levels generally correlated well with increased mRNA and /or protein levels, even if accurate predictions of proteins could not be made. As discussed throughout prosecution, the law does not require the existence of a "necessary" correlation between DNA/mRNA and protein levels, or that protein levels be "accurately predicted." In fact, authors in several of the cited references (cited both, by the Examiner, and by Appellants) themselves acknowledge that there is a general correlation between protein expression and transcript levels and DNA levels, which meets the "more likely than not standard." Therefore Appellants have explored this issue thoroughly throughout prosecution in the vast number of references presented in this case and the evidence should be viewed as a whole.

Regarding the Examiner's contention that references Orntoft *et al.*, Hyman *et al.*, Pollack *et al.* are flawed because, allegedly, their studies were directed highly amplified genes or abundant proteins, Appellants have submitted that PRO269 is significantly amplified (according to the Goddard Declaration) throughout prosecution. Appellants believe that this significantly

amplified DNA would more likely than not result in a higher expression of PRO269 protein, according to the teachings of many references including Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, Bea *et al.*, Godbout *et al.*

Regarding the art exemplified by Sen *et al.*, Appellants' maintain their position that Sen still supports their case for the reasons outlined in their Appeal Brief filed August 29, 2007, which is hereby incorporated by reference. Briefly Appellants maintain that, even if the amplification of the PRO269 gene were due to chromosomal aneuploidy (which Appellants expressly do not concede to), since there is utility for an aneuploid gene at least as a marker for cancer or precancerous cells or damaged tissue, one skilled in the art would find it entirely reasonable that PRO269 is useful in the early detection of lung cancer.

The Examiner contends that the Li article constitutes strong opposing evidence for the presumption that the claimed polypeptides are also overexpressed following gene amplification. Appellants respectfully disagree. The Li article was discussed extensively in the Appeal Brief filed August 29, 2007; these discussions and arguments are hereby incorporated by reference. In the article, genes were considered to be amplified if they had a copy number ratio of at least 1.40. In the instant case for PRO269, as discussed in the Goddard Declaration (of record), an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0 (which is a higher threshold that Li's 1.40). The PRO269 gene showed significant amplification of **2-3.5 fold amplification in 8 primary lung tumors and tumor cell lines**, and thus fully meets the Goddard standard as well as the Li standard. Appellants further note, and it is not surprising that, in the Li *et al.* reference, by using a lower threshold of 1.4 for considering gene amplification, a higher number of genes not showing corresponding increases in mRNA expression were found. Nevertheless, the results of Li *et al.* do not conclusively disprove that a gene with a substantially higher level of gene amplification, such as PRO269, would be expected to show a corresponding increase in transcript expression. therefore Li does not constitute opposing evidence.

Based on Godbout et al., the Examiner requests "that the protein encoded by the PRO269 gene would confer any selective advantage on a cell expressing it." in the Examiner's answer; in other words, the Examiner requests Appellants to show the mechanism by which the claimed protein acts within the cell. However, Appellants respectfully remind the Board that

demonstration of the mechanism is not a requirement for attaining that utility. Appellants believe that such a requirement is a heightened utility standard imposed by the Examiner. In fact, as stated by the Federal Circuit, "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortwright*, 165 F.2d 1353, 1359 (Fed. Cir. 1999). The Federal Circuit has also stated that "[a]n invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is not operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.* 730 F.2d 753,762, 221 USPQ 473,480 (Fed. Cir. 1984)." Hence this rejection is improper.

Collectively, Appellants submit that the Examiner's concerns in this rejection are misplaced and cannot properly form the basis for utility rejections of the present claims.

(5) Appellants have already discussed the references Pennica *et al.* and Konopka *et al.* in great detail throughout prosecution and in their Appeal Brief filed August 29, 2007; these discussions and arguments are hereby incorporated by reference.

Briefly, the teachings of Pennica *et al.* are specific to *WISP* genes, a specific class of closely related molecules. Pennica *et al.* showed that there was good correlation between DNA and mRNA expression levels for the *WISP-1* gene but not for *WISP-2 and WISP-3* genes. The fact that, for two out of three specific molecules there seems to be no correlation between gene amplification and/or mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. As discussed throughout prosecution, the standard is not absolute certainty. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression for genes in general. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression* . . . " (Pennica *et al.*, page 14722, left column, first full paragraph, emphasis added). Accordingly, Appellants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between gene amplification and over-expression of mRNA or polypeptides in most genes, in general.

Similarly, in Konopka *et al.*, the Examiner has generalized a very specific result disclosed by Konopka *et al.* to cover all genes. Konopka *et al.* actually state that "[p]rotein expression is not related to amplification of the ***abl*** gene but to variation in the level of *bcr-ab*l mRNA produced from a single Ph^1 template." (See Konopka *et al* ., Abstract, emphasis added). The paper does not teach anything whatsoever about the correlation of protein expression and gene amplification in general, and provides no basis for the generalization that apparently underlies the present rejection. The statement of Konopka *et al.* that "[p]rotein expression is not related to amplification of the *abl* gene . . . " is not sufficient to establish a *prima facie* case of lack of utility. Therefore, the combined teachings of Pennica *et al.* and Konopka *et al.* are not directed towards genes in general but to a single gene or genes within a single family and thus, their teachings cannot support a general conclusion regarding a correlation between gene amplification and mRNA or protein levels.

In fact, in the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.,* Hyman *et al.,* Pollack *et al.,* overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Appellants submit that when the proper legal standard is applied, one of skill in the art should reach the conclusion, based on the amplification data for the PRO269 gene, that the PRO269 polypeptide is concomitantly overexpressed, and that the present application discloses at least one patentable utility for the claimed PRO269 polypeptides. Accordingly, one of ordinary skill in the art would also understand how to make and use the recited polypeptides for the diagnosis of lung cancer without any undue experimentation.

CONCLUSION

For the reasons given above, Appellants submit that present specification clearly describes, details and provides a patentable utility for the claimed invention. Moreover, it is respectfully submitted that based upon this disclosed patentable utility, the present specification clearly teaches "how to use" the presently claimed polypeptide. As such, Appellants respectfully request reconsideration and reversal of the outstanding rejection of Claims 44-46 and 49-52.

The Commissioner is authorized to charge any fees which may be required, including extension fees, or credit any overpayment to Deposit Account No. **07-1700** (referencing Attorney's Docket No. **39780-1618 P2C33**).

Respectfully submitted,

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Panpan Gao
Reg. No. 43,626

Goodwin Procter LLP
Counsellors at Law
181 Lytton Avenue
Palo Alto, CA 94301
Telephone: 650.752.3100
Facsimile: 650.853.1038